REMARKS

Status of the claims and formal matters

Claims 14, 15, and 27-35 are pending in the instant application. Claims 1-13, 16-19, and 20-26 had been previously cancelled. All pending claims stand rejected.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103, or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendment presented herein should not give rise to any estoppel.

Examiner Interview

Applicant thanks Examiner Javanmard and Supervising Examiner Padmanabhan for participating in the telephone Interview with Paul Prendergast and Marina Heusch (attorneys/agents for Applicant) on November 30, 2010. During said Interview, the Zullino reference was briefly discussed, as was the Examiner's statement, in the pending Office Action (page 3, third paragraph), to the effect that "there is much literature (at the time of filing) that would lead one of ordinary skill in the art to have known that" topiramate has "AMPA antagonist properties'.

Examiner Javanmard kindly agreed to identify all such references in a subsequent Office Action, should the case not be deemed in condition for allowance as a result of the instant response.

Claim rejections under 35 U.S.C. § 103

1. The Examiner has rejected claims 14-15 and 27-33 under 35 U.S.C. § 103(a) as being unpatentable over Chenard (EP 0900568 A2) in view of Zullino (*Progress in Neuro-Psychopharmacol and Biol Psych* 2002) in further view of Dursun, *et al.* (*Canadian Journal of Psychiatry* 2000). Applicant respectfully disagrees.

Chenard does not teach the use of all AMPA receptor antagonists in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy.

The Examiner states that "Chenard teaches the administration of AMPA receptor antagonists for the treatment of dyskinesia which results as a side effect of dopamine agonist therapy given as a therapeutic regimen for Parkinson's disease…" Once again, Applicant respectfully disagrees.

The compounds of the general formula I described in pending claim 14 of the instant application are used to treat dyskinesia manifest as chorea or dystonia in a subject. Prior to the filing date of the application, anticonvulsant sulphamates used in the treatment of epileptic seizures, such as those of the general formula I (for example, topiramate), had also been found to demonstrate efficacy in the treatment of essential tremor. Both epilepsy and essential tremor constitute conditions entirely distinct from the dyskinesia contemplated for treatment in the instant application ([0020], [0022]-[0025]). Yet, unexpectedly, the inventors found that the compounds *do* display efficacy in reducing dyskinesias.

The Examiner relies upon Chenard to demonstrate that it was, at the time of filing of the instant application, already known in the art to employ AMPA receptor antagonists to treat dyskinesia. However, beyond its title "AMPA antagonists for the treatment of dyskinesias associated with dopamine agonist therapy" and similar sweeping statements throughout the reference itself, Chenard provides nothing substantive that shows or even implies that, indeed, AMPA receptor antagonists can be used to treat dyskinesia resulting from the use of dopamine agonist therapy.

The few examples provided in Chenard constitute prophetic examples, i.e., they describe experiments that have not been carried out. Both experiments – the first to evaluate the effect of compounds on AMPA receptor activation-induced $^{45}Ca^{2+}$ uptake in rat cerebellar granule cell cultures and the second to assess the efficacy of the compounds in the treatment of dyskinesias associated with dopamine agonist therapy in the treatment of Parkinson's disease in a rhesus monkey model -- represent standard experimental studies in use at the time of filing. Neither is demarcated with any detail as to how the experimental parameters might be changed to test the very lengthy list of compounds contemplated by Chenard, leaving the person of ordinary skill in the art with an undue amount of experimentation to actually test the compounds in question.

Chenard provides no data whatsoever; nor does the reference provide any reasoned technical explanation to convince the ordinarily skilled artisan that AMPA receptor antagonists can be used to successfully treat dyskinesia resulting from the use of dopamine agonist therapy. Indeed, Chenard teaches nothing substantive about AMPA receptor antagonists in general and dyskinesia beyond its repeated speculation.

Even if the person of ordinary skill in the art had, at the time of filing of the instant application, believed that Chenard was in possession of the invention as claimed therein (in Chenard), i.e., "The use of a compound selected from groups (A), (B), (C), (D), (E), or (F) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy, wherein groups (A), (B), (C), (D), (E), and (F) are defined as follows…", such person would not presume that Chenard was in possession of an invention as seemingly proposed by the Examiner, i.e., the use of any AMPA receptor antagonist in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy.

There is no enabling teaching in Chenard that compounds outside those in groups (A), (B), (C), (D), (E), and (F) are useful in the treatment of dyskinesia associated with dopamine agonist therapy. In this light, Applicant notes that, although the number of compounds speculated by Chenard for use in dyskinesia treatment is substantially large, the list of compounds does not include the compounds described in U.S. Patent Application No. 10/527,761, including, for example, topiramate. Furthermore, the compounds listed in Chenard have significant structural differences from the compounds of the present application. Therefore, one of ordinary skill in the art would not consider a compound claimed in the present application as a compound in group (A), (B), (C), (D), (E), or (F) and would, thus, not be taught to treat dyskinesia with Applicant's compounds.

The Examiner states, in the section entitled "Response to Arguments" of the pending Office Action (page 2, last two paragraphs to page 3, first paragraph) that "Applicant argues that Chenard discloses a large number of compounds as being suitable AMPA receptor antagonists but fails to teach or suggest the use of compound I as an agent for treating dyskinesia (chorea or dystonia). Examiner respectfully notes that Chenard was employed to demonstrate that it is known in the art to employ AMPA receptor antagonists to treat dyskinesia." However, topiramate is a compound that lies well outside of the chemical structures of the compounds

claimed in Chenard as AMPA receptor antagonists. Chenard is not enabled for compounds outside of those groups listed in its claims -- (A), (B), (C), (D), (E), or (F), i.e., it is not enabled for AMPA receptor antagonists in general for treating dyskinesia.

Zullino does not teach that topiramate is an AMPA receptor antagonist.

On page 5 of the pending Office Action, the Examiner states that "Zullino teaches that topiramate is an AMPA receptor antagonist (abstract; discussion)." Applicant respectfully disagrees.

Zullino describes the treatment of three patients undergoing opiate detoxification with topiramate. The topiramate is chosen as an alternative to clonidine, an α_2 adrenergic agonist. The data Zullino describes with respect to topiramate indicates that "it could be rather valuable for opiate withdrawal" (page 1223, column 1, 1st paragraph of Discussion section). Beyond that, there is no reasoned discussion of the mechanism of action of topiramate. The statement the Examiner likely refers to in the Abstract appears to be based on the following statement on page 1222, 1st column, 2nd paragraph of Zullino: "There is some evidence that topiramate acts, among others, through inhibition of kainate-activated (AMPA) receptors (Langtry et al., 1997)." Langtry makes no mention of AMPA receptor antagonism whatsoever. Rather, Langtry, a review of topiramate's properties and efficacy in the treatment/management of epilepsy, states that topiramate "acts via several pharmacological mechanisms, including…inhibition of kainate-mediated conductance." (page 753, "Pharmacodynamic Properties" section). In a subsequent discussion of "Mechanism of Action" on page 756 (first paragraph), Langtry states that topiramate "blocked non-NMDA mediated (kainate-activated) receptors". In fact, the only seemingly relevant (to the pending Office Action) mechanistic information Langtry provides focuses on topiramates potential action on kainate-activated receptors. It would appear that Zullino has simply erroneously equated kainate-activated with AMPA receptors (page 122, second paragraph), since Zullino provides no substantive argument or data of his own to support a statement that topiramate acts through inhibition of AMPA receptors; Zullino appears only to rely on Langtry in this regard.

Applicant now directs Examiner's attention to the recently submitted Bezard Declaration, which Examiner considered in concert with Applicant's previously submitted arguments (of May 26, 2010) and, subsequently, withdrew the Skradski reference, which was likewise used to show

that topiramate was a known AMPA receptor antagonist. Skradski was inconclusive about whether topiramate exerted its effect on AMPA and/or kainate receptors – two distinct receptor types. Applicant submitted Gryder to show that, in fact, topiramate was believed to selectively block the kainate receptor. Indeed, Dr. Bezard specifically stated, in section 6 of his Declaration, that "topiramate was generally considered to act as a kainate receptor antagonist and not as an AMPA receptor antagonist". This statement emphasizes both the fact that AMPA and kainate receptors were believed to constitute two receptor types (rather than the same one, as Zullino appears to state without reason), and that topiramate was thought to act upon kainate (and not AMPA) receptors antagonistically. Dr. Bezard goes on to further emphasize the latter with the following statement in section 10 of the Declaration: "…being very well versed with the state of the art at the time of filing, I maintain that a person in the field would have felt no reasonable inclination to choose topiramate as an AMPA receptor antagonist, since it was widely believed to be a kainate receptor antagonist, and not an AMPA receptor antagonist."

Thus, Applicant's argument that AMPA and kainate receptors were believed to be two distinct receptor types is amply supported by Skradski, Gryder, and the Bezard Declaration. Applicant's argument that topiramate was thought to be a kainate receptor antagonist is likewise amply supported by Gryder and the Bezard Declaration. Zullino offers little more than an unfounded, let alone enabled, statement that topiramate acts, among other, through inhibition of AMPA receptors. The only support Zullino does provide for this statement is a reference to Langtry, which is focused on kainate receptors, and makes no mention of AMPA receptors, in the context of topiramate. Furthermore, Zullino inexplicably appears to equate AMPA with kainate receptors.

Thus, even if the ordinarily skilled artisan were to believe, based on Chenard, that AMPA receptor antagonists in general (i.e., outside of Chenard's compound groups A-F) can be employed in the treatment of dyskinesia, said artisan would not be reasonably motivated to select topiramate as an AMPA receptor antagonist for testing within Chenard's speculated therapeutic use.

Dursun does not teach the treatment of a dyskinesia manifest as chorea or dystonia.

The Examiner states that "…one would be further encouraged that the employment of topiramate in the treatment of dyskinesia would be successful in light of the teachings of

Dursun…Dursun teaches that topiramate is able to improve myoclonic jerks in the patient…" Applicant respectfully disagrees.

The instant claim is directed to a method of treating dyskinesia, wherein the dyskinesia is manifest as chorea or dystonia. Chorea and dystonia are distinct in neurological origin from myoclonus. They are also different phenomenologically, and they respond differently to pharmacological agents.

In particular, myoclonus (myoclonic jerks) describes paroxysmal, quick, lightning-like jerks (contractions) of a muscle or group of muscles akin to epilepsy or convulsions. Indeed, the rapid speed and brief duration of myoclonus are definitive for the disorder. In contrast, chorea is characterized by slow, sinuous writhing and dance-like movements that start in one part of the body and move abruptly, unpredictably, and, often, continuously to another part. In fact, the movements in chorea may merge imperceptibly into purposeful or semi-purposeful acts. Dystonic movements are associated with prolonged bursts of electrical activity in affected muscle(s), causing sustained abnormal postures and bodily contortions.

The underlying neuronal mechanisms of myoclonus are different from the mechanisms underlying the chorea and dystonia referred to in the instant patent application. The primary mechanisms by which chorea and dystonia are produced are known and are different from the mechanisms underlying epileptic or convulsive activity. These fundamental differences can, for example, be borne out by the different responses observed to drug treatment. A pharmacological agent's efficacy for treating myoclonus has no predictive value in relation to its efficacy for treating chorea or dystonia.

Different types of movement disorders can develop, depending on the nature and location of damage to or malfunction of the central nervous system (brain and spinal cord), the nerves, and the muscles. For example, there can occur damage to the parts of the brain that control voluntary movement or the connections between the brain and spinal cord, resulting in weakness or paralysis of the muscles involved in voluntary movements and exaggerated reflexes. There can also occur damage to the basal ganglia, resulting in involuntary or decreased movements. There can also occur damage to the cerebellum, resulting in loss of coordination. And for each of the above-mentioned occurrences of damage, there are distinct movement disorders that may come about as a result of a specific subtype of damage. Thus, the person of ordinary skill in the art would not assume that several movement disorders could, with a reasonable expectation of

success, be treated with a single agent. More specifically, the ordinarily skilled artisan would not reasonably expect that a therapeutic agent (topiramate) used to reduce myoclonic jerks developed in a schizophrenic patient taking clozapine would be therapeutically effective against dyskinesia manifest as chorea or dystonia. Applicant also points out that topiramate was additionally selected for the treatment of the schizophrenic exhibiting severe myoclonus, because topiramate had also been previously observed to have weight loss and mood-stabilizing properties, both specifically beneficial to the patient at hand.

Thus, the combination of Chenard, Zullino, and Dursun does not provide an implicit motivation to, let alone an explicit teaching of, employ(ing) a compound as defined in the instantly pending claim 14 to treat dyskinesia manifest as chorea or dystonia. If an independent claim is non-obvious under 35 U.S.C. § 103, then any claim depending therefrom is non-obvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Having established the non-obviousness of claim 14, claims 15 and 27-33 are, by extension, also non-obvious. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

2. The Examiner has rejected claims 34 and 35 under 35 U.S.C. § 103(a) as being unpatentable over Chenard (EP 0900568 A2) in view of Zullino (*Progress in Neuro-Psychopharmacol and Biol Psych* 2002) in further view of Dursun, *et al.* (*Canadian Journal of Psychiatry* 2000) (all as applied to claims 14-15 and 27-33), in further view of Crossman (*Movement Disorder* 1990). Applicant respectfully disagrees.

The arguments addressing Chenard, Zullino, and Dursun are as iterated above. Crossman sets forth a number of hypotheses regarding the neural mechanisms that mediate levodopa- or dopamine agonist-induced dyskinesia as a side-effect of the treatment of parkinsonism. Crossman does not, however, cure the defect identified above by Applicant with respect to Chenard, Zullino, and Dursun as references cited as rendering obvious the invention as claimed. In other words, Crossman does not provide any indication that topiramate acts as an AMPA receptor antagonist. Thus, its combination with the other three references does not support the Examiner's allegation of obviousness of the subject-matter of claims 34 and 35.

In view of the above-presented arguments, Applicant respectfully requests that the Examiner withdraw the presently pending 35 U.S.C. 103 rejections.

CONCLUSION

Applicant requests a telephone Interview with the Examiner to discuss the instant Office Action response, should the Examiner believe such a conversation would be beneficial and could advance the prosecution of the application.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

/Marina Heusch/

Date: December 21, 2010

Marina I Heusch, Ph.D., Reg. No. 47,647
Agent for Applicant
Swanson & Bratschun, L.L.C.
8210 Southpark Terrace
Littleton, CO 80120
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

S:\ClientFolders\0206 (Mewburn)\MOTAC\MO.04\Response to 10 04 2010 OA.doc